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Improving Post-Discharge Outcomes in Acute Heart Failure

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Introduction

The global burden that acute heart failure (AHF) carries has remained unchanged over the past several decades (1). European registries (2–5) showed that 1-year outcome rates remain unacceptably high (Table 1) and confirm that hospitalization for AHF represents a change in the natural history of the disease process(6). As patients hospitalized for HF have a bad prognosis, it is crucial to utilize hospitalization as an opportunity to: 1) assess the individual components of the cardiac substrate; 2) identify and treat comorbidities; 3) identify early, safe endpoints of therapy to facilitate timely hospital discharge and outpatient follow-up; and 4) implement and begin optimization guideline-directed medical therapies (GDMTs). As outcomes are influenced by many factors, many of which are incompletely understood, a systematic approach is proposed that should start with admission and continues through post-discharge (7).

This review provides practical recommendations on HF management during the time of hospitalization and aims to summarize key lessons from clinical trials and registries in AHF (Table 2).

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Post-discharge outcome in AHF

Mortality remains the most important outcome considered in clinical trials and registries. Recent international RCTs (8, 9) consider 180-day mortality, while registries (4, 5) report 1-year mortality. All-cause-mortality includes HF–related and other cardiovascular and non-cardiovascular mortalities. This may be particularly important in patients with HF and preserved ejection fraction (HFpEF), a clinical setting where comorbidities have an important impact on outcomes. Although, cardiovascular mortality or HF-related mortality may be more appropriate to evaluate the efficacy of new HF therapies, these outcomes need adjudication. Ascertaining the cause of death is difficult in a disease with multiple cardiac and non-cardiac comorbidities (10).

Hospitalization for HF is clinically meaningful to patients, physicians, and regulators, and correlates with disease progression (11). Since approximately half of re-hospitalizations are not related to HF(12), all-cause hospitalizations is a comprehensive outcome that can be used to determine whether HF hospitalization will be reduced by an intervention and not negated by the competing risk of other CV or non-CV hospitalizations. HF hospitalizations can be precipitated by a variety of factors, and their relative importance as a cause of hospitalization can be hard to detect. Also, hospitalization is a disposition not a clinical diagnosis, and the decision to hospitalize can be driven by external factors unrelated to the patient's clinical status (e.g. variability across different healthcare systems, local availability of hospital facilities, day of the week or time of day the patient presents, or physician and patient local practices) (13). Thus, a consistent definition for HF-hospitalization should be implemented across clinical trials and registries. An Expert Consensus (10) defined HF-hospitalization as more than 24 hours in-hospital stay caused by worsening of HF symptoms and/or signs requiring an increase in the dose or frequency of administration of oral medications or new administration of IV therapy or new initiation of renal replacement therapy or mechanical circulatory support.

Recurrent hospitalizations are a common occurrence in patients with HF, accounting for 42% of the total admissions (14). 'Time to first event' analysis did not consider subsequent HF hospitalizations, suggesting that methodologies accounting for repeated events should be used to quantify the patient's journey throughout the follow-up period (15).

Similar to mortality, RCTs and registries consider 180-day and 1-year hospitalization. Thirty-day readmission is not an adequate outcome for HF due to a potential disconnect between early readmission and short-term post-discharge mortality caused by the competing risk between early readmissions and 30-day mortality (16).

The therapeutic goal in HF patients is not limited to prolonging survival, improving the quality of life gained is equally important. Many instruments are available to prospectively collect patient-reported quality of life data, but the Kansas City Cardiomyopathy Questionnaire (KCCQ) has shown validity and responsiveness to change (10). KCCQ has been widely used as a measure of patient-related outcome and was shown to be a relevant prognostic factor predicting readmission and mortality and incrementally added information for risk stratification when used before discharge or at 1-week after discharge (17, 18).

Other measures to assess functional status and exercise capacity, as serial six minute walking test (6MWT) demonstrated feasibility as a “patient centric” endpoint in AHF patients (19). Performing 6MWT was reproducible, safe and feasible and seems to relate to 30-day events (19).

Address precipitants

Identification of acute precipitants with subsequent initiation of specific treatments should be done within the first 60–120 minutes after initial evaluation (20). AHF precipitants are diverse (Figure 1) but the vast majority can be identified based on a standard admission history and physical examination, supplemented with an electrocardiogram (ECG), basic laboratory and radiographic data obtained in the emergency department. Only in 9% of cases, clinical decompensation can occur without a clear identifiable precipitant (6). When inappropriately addressed, some precipitants may insidiously persist throughout hospitalization and post-discharge and contribute to the pathophysiology of the vulnerable phase.

Treat beyond clinical congestion

The most common driver for hospitalization and repeated hospitalizations is congestion (21). Data from recent registries revealed that about 15–20% of AHF patients are discharged with persistent signs/symptoms of congestion and/or minimal or no weight loss (5). Even more patients are discharged with relief of congestive signs but with persistently high left ventricular filling pressures as demonstrated by elevated natriuretic peptides (NPs), provoked orthopnea, paradoxical changes of SBP in orthostasis or at Valsalva maneuver and a poor 6MWT (21–24).

This group of patients with persistent hemodynamic congestion, have readmission and mortality rates higher than in those adequately decongested (25). Treating congestion beyond signs and symptoms should be the essential target, and patients who maintain lower filling pressures have better survival (26).

The strategies employed to deplete congested patients include: varying the type and dose of diuretic, initiating vasopressin antagonists, and in-hospital use of ultrafiltration, digoxin, and vasodilators (27).

Treating congestion should consider the pathophysiology contributing to the congestion (Figure 2). Beside overall volume overload there is also redistribution of extracellular fluid into the vascular bed, increasing effective circulating volume and cardiac filling pressures (28). This scenario may be better addressed with the use of vasodilators, as the main goal is to reduce intravascular pressure. Nitrates are the most commonly used and were proven effective for control of symptoms with better in-hospital outcomes (29). However, two recent RCTs, RELAX-AHF-2 (30) and TRUE-AHF (9), investigating vasodilating agents serelaxin, and ularitide, although decreased NPs levels and improve hemodynamic congestion, have both failed to improve 180-day clinical endpoints.

Loop diuretics (furosemide, torasemide, bumetanide) are the mainstay for decongestive therapy. Notably, HF shifts the dose-response curve for loop diuretics downward and to the right, necessitating a higher starting dose to achieve the same level of sodium excretion (31). Chronic furosemide treatment may induce “nephron adaptation,” a reactive increase in sodium transport capacity in the tubular segments situated distally to site of action of furosemide (32). This may result in a reduced natriuretic response at conventional IV diuretic doses, requiring an increased dose of IV diuretics to obtain the expected clinical response.

In a post-hoc analysis of the CHAMPION trial evaluating the transition from chronic status to AHF, by invasively monitoring in ambulatory setting the pulmonary artery pressures, demonstrated that the most common adjustment of medication in the improved survival arm was change of diuretic dose (33).

Several prior studies enrolling patients with AHF have demonstrated an association between higher diuretic dose and greater risk for adverse clinical outcomes, with putative mechanisms of harm related to arrhythmic death due to electrolyte depletion, hypovolemia, and increased neurohormonal activation (34–36).

In contrast, in the EVEREST trial, higher diuretic doses were associated with improved survival in patients with evidence of hemoconcentration in response to therapy, and higher average diuretic doses during the first 3 days of hospitalization were not associated with increased risk for the 30-day combined endpoint of all-cause mortality or HF-readmissions (37, 38). These results are concordant with a report from the ALARM-HF (Acute Heart Failure Global Survey of Standard Treatment) registry, which reported no association between in-hospital diuretic dose and 30-day mortality (39).

The assessment of venous congestion is particularly challenging in patients with HFpEF, who are frequently obese with age-related non-cardiac comorbidities. A recent study (40) showed that in acute conditions, HFpEF and HFrEF presented with a comparable state of venous congestion. Similarities in the level of systemic congestion between acute HFpEF and HFrEF may suggest the use of similar decongestive therapies in the initial phase, especially with regard to diuretics and vasodilators.

Studies have shown clinical benefit with torasemide, but the populations were investigated in the chronic setting and benefits were not reproduced in a contemporary cohort of AHF patients (41, 42). For practical purposes, torasemide is reserved for patients who required high daily doses of furosemide (>120mg t.d.) or in patients with suspected gut edema and poor bioavailability of oral Furosemide (43).

Although ultrafiltration did not prove superior survival benefits compared to fixed dose loop diuretics, hospitalization and repeated hospitalizations were reduced in the initial UNLOAD trial (44). In addition, CARRESS-HF (45) subsequently found that patients with persistent congestion and cardio-renal syndrome could be decongested comparable well with a stepped pharmacologic strategy (i.e. diuretics, vasodilators, and/or inotropes) compared to pure ultrafiltration. Ultrafiltration provided more rapid weight loss, effect not beneficial in

patients with worsening renal failure or when volume shift is the predominant mechanism for HF decompensation (45).

Diuretic resistance is a relevant clinical issue and another strategy to overcome it is the use of vasopressin antagonists, as it may allow less escalation of loop diuretic dose and preserve renal function. However, in two recent trials TACTICS (46) and SECRET of CHF (47), the addition of tolvaptan to a standardized furosemide regimen did not improve dyspnea, despite greater weight loss and fluid loss.

In the ATHENA-HF trial (48), mineralocorticoid receptor antagonists were investigated as a mean to promote adequate decongestion and mitigate diuretic resistance in decompensated HF patients. Although well tolerated, high dose spironolactone did not improve the clinical congestion score, dyspnea assessment, net urine output or net weight change, and did not improve survival or hospitalization (48). New RCTs, CLOROTIC (49) and TRANSFORM-HF(50), are further investigating whether using torasemide or adding thiazides could be beneficial.

At this time, there is no clear pathway for decongestive therapy to improve outcomes, but a more individualized strategy including reduction in NPs> 30% during the hospital stay and hemoconcentration targeted diuresis with avoiding hypotension, should be considered.

Treat underlying cardiac abnormalities

A model (Figure 2) that aims to address the significant contributors to development of AHF includes identifying and treating: hypertension, coronary artery disease, myocardial disease, electrical abnormalities, valvular disease, pericardial disease, comorbidities, and noncompliance (51).

Some patients may have severely depressed EF but substantial contractile reserve demonstrated at the time of stress Echo and indicating a possibility for recovery with effective medical therapy or high-risk cardiac surgery (52). Identifying dysfunctional but viable myocardium, is the key to focus resources in those patients that have the real potential to recover. However, in STICH trial (53) the assessment of myocardial viability did not identify patients with a differential ten-year survival benefit from CABG, as compared with medical therapy alone, but the techniques used to assess viability/contractile reserve were diverse.

Only a minority of patients represents true end-stage HF, but even in these patients the prognosis can be changed by an adequate selection for heart transplantation or left ventricular assist devices (LVADs). The REMATCH study showed long term survival benefits in patients who received LVADs as destination therapy as compared to medical therapy (54).

Right Ventricular Dysfunction (RVD) is a common finding in AHF (25%), and carries a dismal prognosis especially when associated with pulmonary hypertension (PH) (55). Right HF may be caused by RVD itself or by RV remodeling secondary to pressure or volume overload, including annular dilatation causing tricuspid insufficiency, supplementary

contributing to RV dysfunction (Figure 3). Afterload mismatch in the setting of PH is the most common case scenario for RVD in both HFpEF(56) and HFrEF(57). In HFpEF, independent of PH, the direct effects of comorbidities such as obesity, hypertension and diabetes mellitus should be considered(56).

Patients with RV failure may be preload-dependent, but excessive volume overload is a major driver of decompensation, deterioration of RV function and multi-organ dysfunction (e.g. hepatic, renal, and splanchnic dysfunction) (56, 57), these patients requiring more aggressive decongestion, commonly using diuretics.

Understanding of RV-pulmonary circulation coupling is of particular importance, especially in HFpEF, because conventional systemic vasodilators used to treat left-sided heart failure have no beneficial effect on the right heart (57).

In the past decade evidence has accumulated that led to a paradigm shift suggesting myocardial dysfunction has different mechanisms in HFpEF versus HFrEF. A pro-inflammatory state induced by comorbidities is at the center of this hypothesis (58). This further induces myocardial remodeling with concentric hypertrophy and myocardial dysfunction due to endothelial senescence and dysfunction(58).The vast majority of HFpEF patients do not have any specific genetic, pericardial, or valvular abnormality that is currently of clinical significance. This has been translated into targeted interventions based on identifying a specific clinical variant (lung congestion, chronotropic incompetence, pulmonary hypertension, atrial fibrillation) and a predisposition phenotype, which accounts for the main comorbidities (59).

Although targeting fibrosis is a logical hypothesis in HFpEF, two RCTs investigating the aldosterone antagonist spironolactone in HFpEF, TOPCAT and Aldo-DHF, failed to improve clinical outcomes or symptoms (60, 61).

Other trials targeting PHT in patients with HFpEF did not improve clinical endpoint or have been associated to decrease of SBP or worsening of congestion (62–64).

Treat non-cardiac comorbidities (NCC)

Following a HF-hospitalization, 40% of all-cause deaths and re-hospitalizations are due to NCC (12). Each comorbidities, with its specific pathophysiology carries a different impact on mortality and hospitalizations, and should be specifically addressed.

Diabetes mellitus (DM) is present in approximately 40% of patients hospitalized for HF and is associated with worse post-discharge outcomes, independent of the LVEF (65). In a large multinational cohort of patients with AHF, blood glucose concentrations at presentation are powerfully prognostic for in-hospital, 30-day and 1-year mortality, independent of a diagnosis of DM (66). However the most adequate strategy for glucose control in AHF patients is not known, since tight glucose control, investigated in GLUCONTROL (67) and NICE-SUGAR (68), was not associated with improved outcomes in critically ill patients. Also, as insulin causes fluid retention, management of glucose control in AHF may be challenging (68).

The two medications proved not to harm these patients are metformin and empaglifozin. Empaglifozin is presumed to act as a diuretic and has shown a survival benefit in HF patients with type 2 DM on top of metformin, in the EMPAREG trial (69). Limitations exist as no data on the severity or chronic vs. acute status of HF patients are so far available. The EMPEROR-HF clinical trial program will further evaluate the safety in chronic setting in both HFrEF (70) and HFpEF (71) patients. At this point it is not considered a class effect, although the CANVAS trial investigating canagliflozin reported a significant decrease in HF readmissions (72).

Chronic obstructive pulmonary disease (COPD) is present in approximately 10%–15% of hospitalized AHF patients. A concomitant diagnosis of COPD at the time of HF-hospitalization identified an almost 30% increase in the risk of new hospitalization in the subsequent year, but had no significant independent impact on 1-year total mortality (73). The beta blocker (BB) use is not a contraindication in COPD, especially for cardio-selective BB, and the beneficial effects in reducing mortality are still present (74). Inhaled beta-2 agonists (which have little effects on cardiac function) should be added when needed in patients who are treated with BB (75). Diuretics should not be overused in the acute setting, in order to avoid metabolic alkalosis, which may deteriorate respiratory drive (75).

Hepatic dysfunction is present at admission in 10–30% of patients with AHF (76) and most commonly is represented by acute liver injury. Hepatic injury in AHF may be either due to low cardiac output, also known as acute cardiogenic liver injury/hypoxic injury and should be managed with inotropes, or as congestive hepatopathy when cholestasis is encountered, pattern reflecting increased right atrial pressures and requiring high diuretic doses (76).

Iron deficiency (ID) is a clinically relevant comorbidity independent of anemia. Previous studies enrolling chronic HF patients (77, 78), reported ID to be associated to with impaired symptoms, functional limitations and worse survival and suggested ID as an important therapeutic target: intravenous iron administration improves morbidity and symptoms. In a recent study enrolling patients with AHF, the reported prevalence of ID was 68.6% in men and 75.3% in women (79). Of note, ID in this acute setting was not related to HF severity, underlining the need for ID screening at the time of hospitalization for all patients with worsening HF.

There is an urgent need for integrated care in patients with HF and NCCs and further clinical investigations and educational initiatives from both cardiology and other specialties will be essential to enhance the quality of treatment and improve the outcomes of these patients.

Initiate disease modifying therapies

Hospitalization provides the opportunity to implement guideline-directed medical therapies (GDMTs). However, it has been repeatedly observed that a sizeable proportion of HF patients do not receive evidence-based treatments or the dosage of medications is usually suboptimal (80).

A risk-treatment paradox has been identified for HF, whereby higher-risk patients are less likely to receive recommended therapy. Higher-risk patients may have a higher prevalence of

contraindications to therapy, rendering them ineligible for evidence-based therapy (i.e. evidence gap). However, it may also reflect higher-risk patients being less likely to receive therapy even when eligible for treatment (i.e. treatment gap) (81). Optimizing HF outcomes will require the development of effective strategies to ensure that eligible high-risk patients receive all appropriate therapies. One of the obstacles limiting the early prescription of GDMTs at the time of discharge from a HF-hospitalization might be related to the adverse effects of these drugs while patients are still fragile. Maintenance or introduction of GDMTs may be challenging in patients with AHF who had dyspnea and other signs and symptoms including altered heart rate and/or blood pressure and often deteriorated kidney and/or liver function. IMPACT-HF (82) was an early study that showed benefit with initiation of carvedilol before discharge. In a recent study(83), administration of GDMTs at hospital discharge is associated with better survival of AHF patients regardless of EF or associated comorbidities. Deferral for only one month of all three classes of treatment, even in a patient with low-risk HF, carries an absolute mortality risk of around 1% per month (84).

Several other studies are currently testing accelerated up-titration of GDMTs, immediately after stabilization and before discharge (85–88).

Digoxin may have a unique role in the vulnerable phase following HF hospitalization and has been associated with reductions in 30-day all-cause readmissions (89). In high-risk patients, digoxin also reduced the composite of all-cause mortality or hospitalization, while withdrawing digoxin leads to an increased risk of subsequent HF decompensation (90).

Use of devices has significantly improved the prognosis of HF patients. Increased QRS duration is an independent predictor for post-discharge mortality in hospitalized patients with HFrEF (91) and early identification of CRT candidates during the hospitalization is crucial to prevent continuous deterioration of cardiac function. Although current guidelines recommend postponing a device implant after an AHF hospitalization, the best strategy is yet unknown. No evidence exists for beneficial use of ICDs in the acute setting and there is even concern for harm, as it might be a driver for re-hospitalizations(92).

Although current therapies have addressed hemodynamics, neurohormonal modulation, and electrophysiological aspects of HF, these therapies have not targeted the metabolic needs of the failing heart. Myocardial metabolism is altered in HF, and substrate utilization switches from mostly free fatty acids (FFAs) to glucose with decreased high-energy phosphate content (93). Despite these alterations, there are currently no approved drugs that directly target cardiac metabolism in HF patients (94). Trimetazidine, a modulator of FFAs metabolism, ameliorated symptoms and echocardiographic endpoints in a small trial in chronic HF. However, evidence of benefit in AHF is lacking (95).

Finally, coenzyme Q10 (CoQ-10) deficiency, implicated in the long-term prognosis of HF may be a rationale target for intervention studies. One trial investigating CoQ-10 supplementation in chronic HF patients has shown benefit on clinical endpoints including mortality (96).

Prognosis

One of the major goals of AHF risk-stratification is to match the risk profile of the patient with the type and intensity of care. In-hospital assessment of prognosis is based on numerous variables that have shown in trials and registries to have independent value in predicting mortality. A comprehensive assessment in these patients is necessary to identify prognostic characteristics that may become possible therapeutic targets. In RCTs and registries, the predictive factors for post-discharge mortality included age, history of previous hospitalization, congestion, systolic blood pressure, heart rate, QRS duration, renal function, markers of organ injury, and non-cardiac comorbidities (such as diabetes, cerebrovascular disease, chronic obstructive pulmonary disease, liver cirrhosis, and iron deficiency)(97).

Follow up visit during vulnerable phase

The transition from the in-hospital to the outpatient setting can be an especially vulnerable period, and multiple cardiac and non-cardiac factors contribute to its occurrence (Table 3). Despite of the apparent clinical and hemodynamic improvement, the early post-discharge period patients often experience worsening signs and symptoms of congestion and marked hemodynamic, and renal function deterioration (98). Some of these abnormalities have a prognostic significance influencing early mortality and/or re-hospitalization (98). Therefore, a follow-up visit within 1 to 2 weeks is recommended (99). Proposed components of this follow-up visit should ideally include monitoring of signs and symptoms of HF, assessment of volume status and SBP, measurement of renal function and possibly NPs. This follow-up visit is an ideal opportunity to initiate or up-titrate GDMTs (100).

Although, there is no prospectively validated risk score to accurately identify patients at high-risk for mortality and early readmission, some variables collected at discharge including residual congestion, persistent renal dysfunction and insufficient decrease in NPs are associated with a higher likelihood of adverse outcome early after discharge (101). Furthermore, a retrospective analysis of EVEREST identified the components of the 1-week follow-up visit associated with increased long-term mortality: a targeted physical examination, identification of high BNP, low serum sodium, renal function and quality of life status assessed by KCCQ(17).

Raise the bar for the performance measures

Hospitalizations remain relevant as a countable cost and as a marker for disease severity, but there are limits to use hospitalization as single metric for quality. If penalties for hospitalizations are too severe, unintended consequences may include competition for the lowest-risk patients, or delayed hospitalization of high-risk patients. Also, a very strict approach for HF hospitalization has paradoxically increased mortality(102), or may shift care patterns with increased ED visits (13).

While other metrics are intuitive as a surrogate for quality, these require prospective validation. These include planning early post-discharge follow-up for high-risk patients or including them in multidisciplinary care programs (103). However, these performance

interventions should not divert attention from understanding the underlying pathophysiology of conditions that culminate in hospitalizations for HF. The only intervention so far shown to improve post-discharge outcomes is GDMTs for chronic HF prescribed during admission (104).

Design and develop appropriate research

Although many trials investigating short-term infusions have been performed in AHF patients, to date there is no approved therapy known to reduce mortality or readmission risk. The main criticism with the prior trials is that they have exclusively focused on short-term therapy during hospitalization (i.e. Stage A and B trials) to improve early symptoms that are already markedly improved by standard therapy (105). Furthermore, as the physiological changes in these patients, occurs days to weeks before admission, whereas most adverse outcomes occur post-discharge, it is questionable whether this short-term approach alone will completely impacted long-term pathways. Another approach is to consider period surrounding AHF as a marker of high-risk and focus on long-term disease modifying novel therapeutic approaches initiated during hospitalization or soon after discharge (i.e. Stage C trials) (6).

Conclusions

The data collected from future clinical trials and registries serve to better understand the clinical course of AHF patients and to identify unmet needs in order to refine management algorithms and to guide further research.

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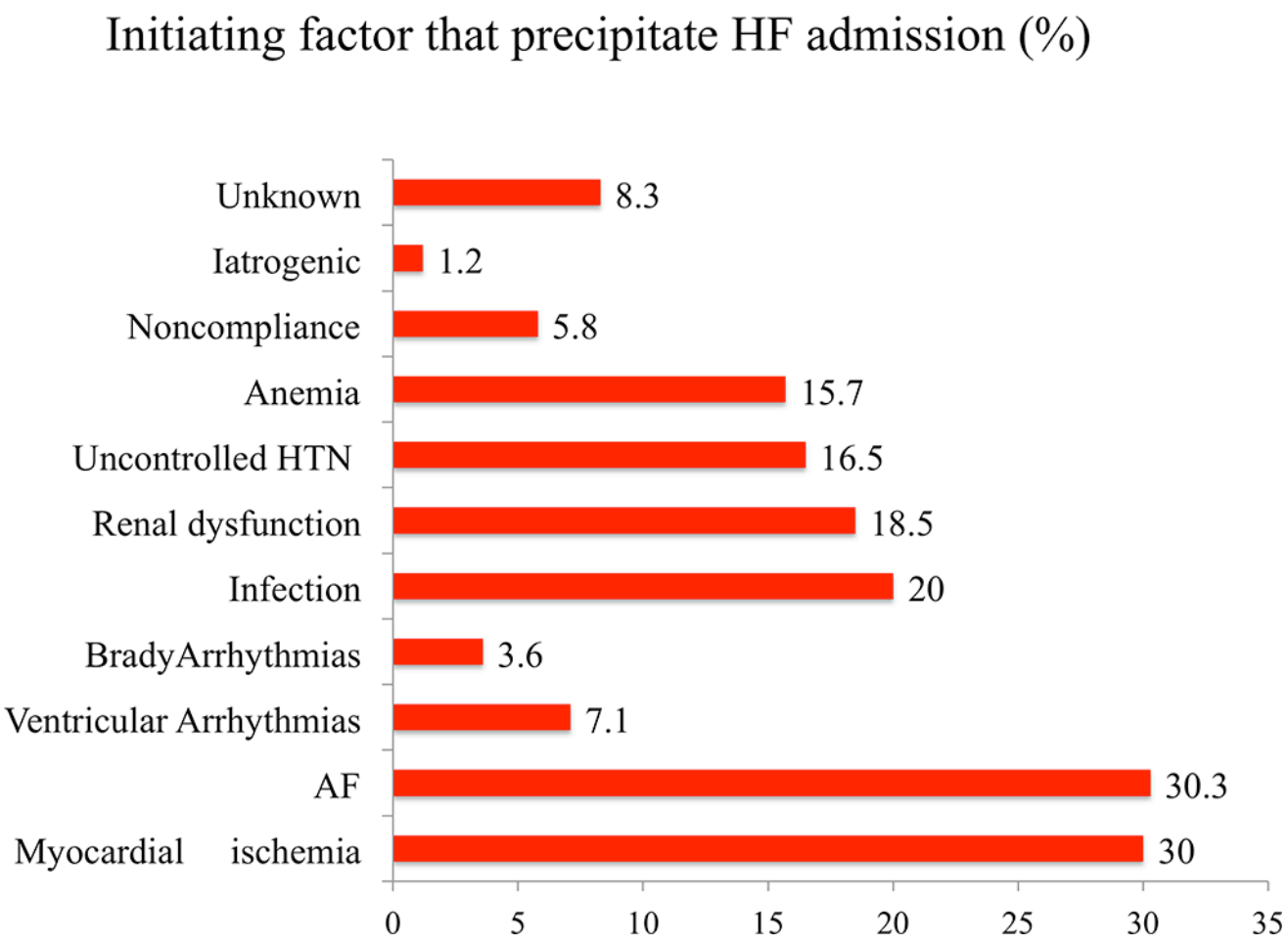

Figure 1.
Initiating factors that precipitate HF admission (5).

Abbreviations: AF=atrial fibrillation; HTN=hypertension.

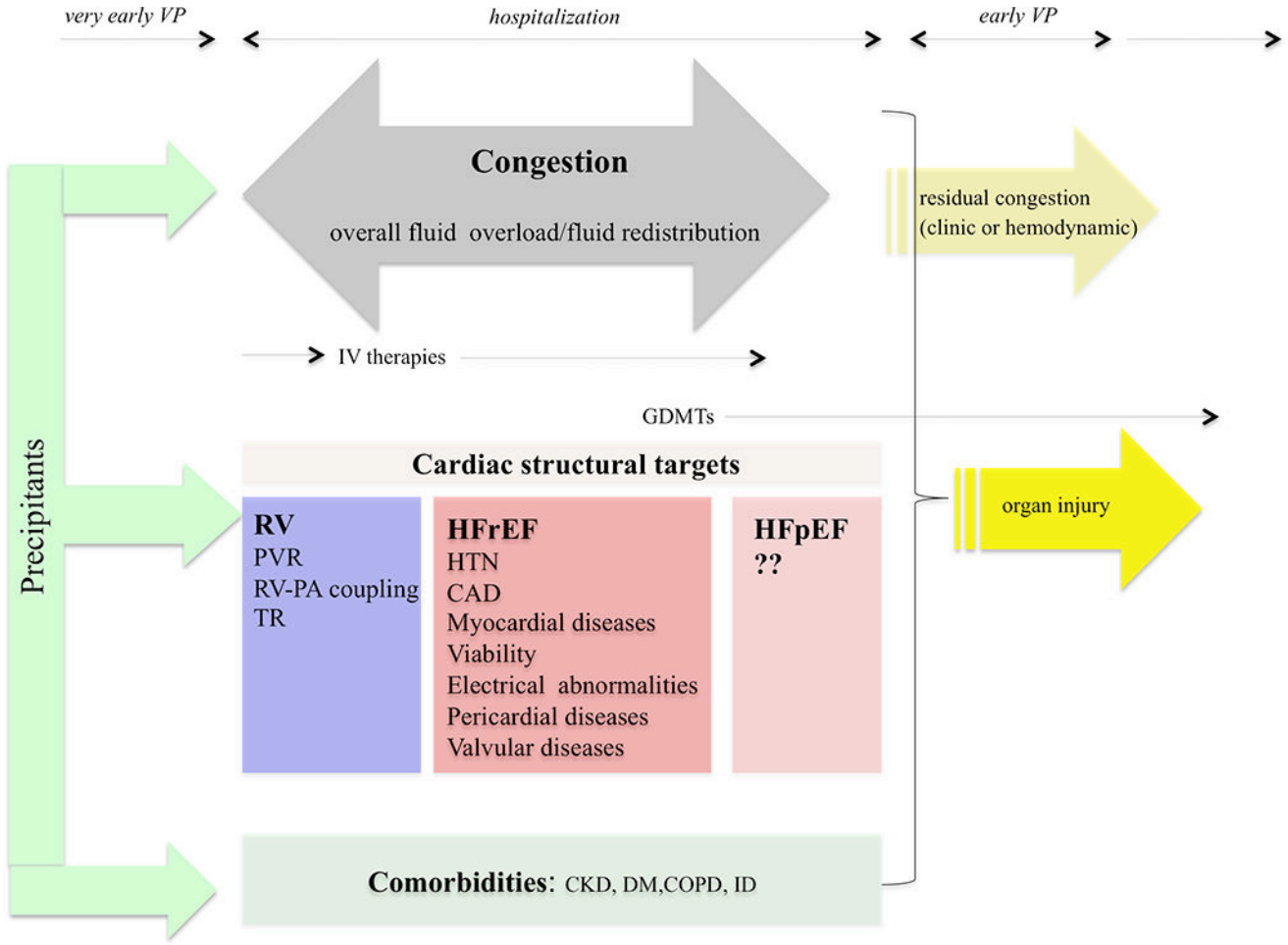

Figure 2.

Comprehensive assessment during hospitalization and vulnerable period with identification of cardiac and non-cardiac structural targets.

Abbreviations: CAD=coronary artery disease; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; DM=diabetes melitus; ID=iron deficiency; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; HTN=hypertension; PA=pulmonary artery; PVR=pulmonary vascular resistances; RV=right ventricle; TR=tricuspid regurgitation

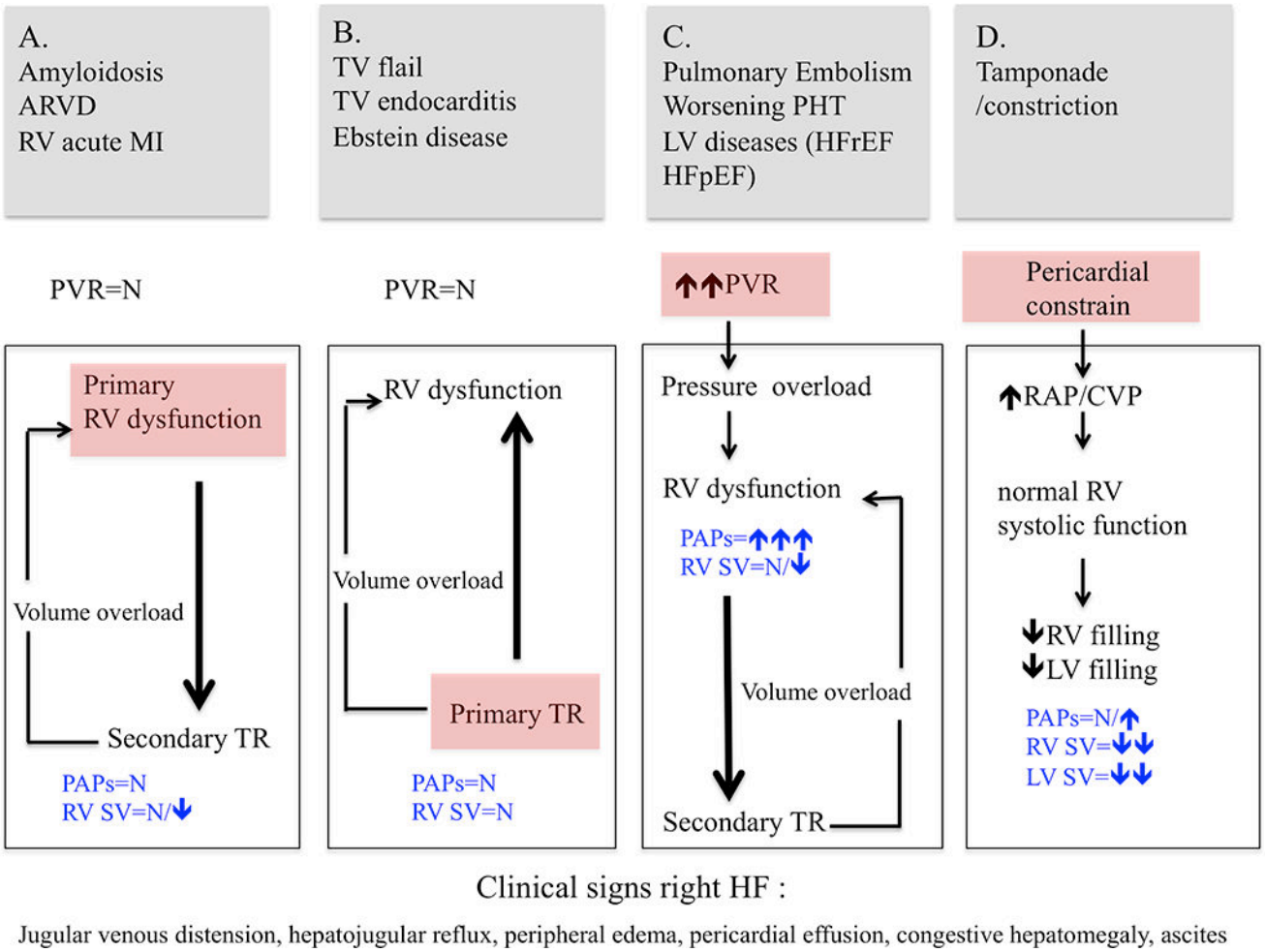

Figure 3.

Pathophysiology of right ventricular dysfunction and right ventricular failure with the four hemodynamic models.

Abbreviations: ARVD=arrhythmogenic right ventricular dysplasia; CVP=central venous pressure; MI=myocardial infarction; PAP=pulmonary artery pressure; RV SV and LV SV =right and left stroke volume; PHT=pulmonary hypertension; PVR=pulmonary vascular resistance; RAP=right atrial pressure; TR=tricuspid regurgitation; TV=tricuspid valve.

Table 1

One-year mortality rate and one year all cause and HF related hospitalizations in European registries with different enrollment strategies. Study acronyms, methodology, time frame of enrollment and in-hospital ACM in overall cohorts are presented in the first row.

	EHFS II[2] ***(2004–2005)*** **N=3580 133 sites 20pts/site in-hospital ACM=6.7%**	**ESC-HF pilot[3]** ***(2009–2010)*** **N=1892 137 sites periodic consecutive in-hospital ACM=3.8%**	**IN-HF[4]** ***(2007–2009)*** **N=1855 61 sites 1y-consecutive in-hospital ACM=6.2%**	**ESC-HF-LT registry[5]** ***(2011–2015)*** **N=6629 211 sites periodic consecutive in-hospital ACM=5.5%**
One-year all cause mortality (%)	20.5	17.4	24.0	26.7
All cause hospitalizations(%)	-	43.9	30.7	44.4
HF related hospitalizations (%)	-	24.8	15.8	25.9
All-cause death or HF hospitalization (%)	-	35.8	-	-42.3

Abbreviations: ACM=all cause mortality; HF=Heart Failure
EHFS II = European Heart Failure Survey II
ESC-HF pilot=Heart Failure pilot study
ESC-HF-LT registry=ESC Heart Failure Long Term Registry
IN-HF = Italian Registry on Heart Failure Outcome

Table 2

Key lessons in acute heart failure registries and trials

1	Understand post-discharge outcomes • Mortality • Re-hospitalizations • Quality of life
2	Address precipitants
3	Treat beyond clinical congestion • Clinical vs hemodynamic congestion • Mechanisms: systemic vs redistribution • Strategies for decongestion: Furosemide, Torasemide, add Thiazide, Ultrafiltration, AVP antagonists, MR antagonists
4	Treat underlying cardiac abnormalities • 8 axis model • Understanding myocardial viability • Understanding HFpEF • Understanding RV
5	Treat non-cardiac co-morbidities
6	Initiate disease modifying therapies early in the course of disease. • use digoxin and MR antagonists • identify candidates for devices • address metabolic needs
7	In-hospital assessment of prognosis
8	Follow-up during vulnerable phase
9	Rise the bar of the performance measures
10	Design and develop appropriate research • Conduct Stage C trials

Abbreviations: AVP-arginine vasopressin; HFpEF-heart failure with preserved ejection fraction; MR-mineralocorticoid receptor; RV-right ventricle.

Table 3

Factors influencing Vulnerable period

Cardiac factors

- failure to relieve clinical congestion during hospitalization
- persistence of hemodynamic congestion
- post-discharge persistence of multi-organ injury(Troponin)
- persistence of precipitants (even subclinical)

Non-cardiac factors:

A. Patient related
- poor medical compliance

B. Physician/hospital related
- Premature discharge
- Poor medical education
- Insufficient follow-up
- Unrecognized adverse drug effects
- Complications following procedures
- Worsening of obscure comorbidities
- Silent nosocomial infections

C. System related
- Not recognizing vulnerable phase as high risk phase
- No reimbursement for early follow up visit
- Inadequate incentives/penalties